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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/657,703	PEBAY ET AL.	
	Examiner	Art Unit	
	Daniel C. Gamett, PhD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-108* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-9, 13-16, 41, 63, 65-70,79, 81-86, 90-93, and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-108* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/28/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 2,10-12,17-40,42-62,64,71-78,80,87-89,94 and 96-108.

DETAILED ACTION

1. Applicant's election with traverse of claims 3, 65, 81, and 95 in the reply filed on 08/08/2005 is acknowledged. Upon further consideration, the elected claims are hereby rejoined with the claims of Group I (1,4-9, 13-16, 41, 63, 66-70,79, 82-86, 90-93). The requirement for restriction between the aforementioned claims and all other Groups of claims is still deemed proper and is therefore made FINAL.

2. Claims 2, 10-12, 17-40, 42-62, 64, 71-78, 80, 87-89, 94, and 96-108 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 08/08/2005.

3. Claims 1, 3-9, 13-16, 41, 63, 65-70,79, 81-86, 90-93, and 95 are under examination in this Office Action.

Claim Objections

4. Claim 41 is objected to because of the following informalities: Claim 41 is dependent from nonelected claim 17. Applicant is required to cancel or amend the claim to remove dependency from nonelected claims. Appropriate correction is required.

5. Claim 81 objected to because of the following informalities: Claim 81 currently recites a LDL receptor. Applicant's intent was most likely "LPL" receptor. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 3-9, 13-16, 79, and 82-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Use of the term "spontaneous differentiation" in claims 1 and 79 renders these independent claims ambiguous. While the differentiation of cells *in vitro* in the absence of known factors may be considered "spontaneous", the claims are not limited to this context. Differentiation that occurs in standard culture conditions in the presence of serum might be viewed as "spontaneous" or as being evoked by factors in the serum and therefore not spontaneous. Likewise, differentiation of a stem cell *in situ* might be stimulated or evoked by local stimuli and yet still be considered "spontaneous" in the absence of purposeful human intervention. Therefore, the metes and bounds of claims 1 and 79 are not clear. Claims 3-9, 13-16, and 82-86 are indefinite as they depend from an indefinite base claim.

8. Furthermore, claims 7-9, 68-70, and 84-86 are indefinite as they recite "or functional equivalents thereof". As no particular function is recited, any compound that may be viewed as being functionally equivalent to the recited compounds in any assay or context would meet the limitations of these claims. For example, S1P and dihydro-S1P appear to be functional equivalents of one another in the experiment shown in figure 2, and yet dihydro-S1P was chosen for study because it was known to mimic only the receptor-dependent effects of S1P (section

[0257]). So S1P and dihydro-S1P may or may not be functional equivalents, depending on the context. Similar ambiguity would exist for any analog of the recited compounds. Thus, the metes and bounds of these claims are not clear.

9. Claim 13 provides for the use of TNF alpha, NGF, a muscarinic acetylcholine agonist, or a serum or phorbol ester. Claim 41 provides for the use of a medium comprising an agonist of a LPL receptor. Claims 79, 81-86, 90-93, and 95 provide for use of an agonist of a LPL receptor. Claim 95 provides for use of a ligand of a class III tyrosine kinase receptor. In each claim, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

10. Claims 13, 41,79, 81-86, 90-93, and 95 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1, 3, 5-9, 13-16,79, 81-86, and 90-92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for inhibiting differentiation of stem cells, which method comprises incubating the stem cell in the presence of

S1P or dihydro-S1P, does not reasonably provide enablement for methods for enhancing differentiation, which method comprises incubating the stem cell in the presence of an agonist of a LPL receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

13. The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the

prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claims are drawn to methods for modulating spontaneous differentiation of stem cells, which method comprises incubating the stem cell in the presence of an agonist of a LPL receptor. The specification indicates [0030] the term "modulating the differentiation of a stem cell" includes the inhibition or enhancement of cellular differentiation. The term also includes partial inhibition or enhancement of cellular differentiation.

The state of the prior art and the predictability or lack thereof in the art: The art indicates that LPL receptor agonists, S1P and LPA stimulate proliferation and LPA stimulates neurosphere formation in cultured neural stem cells (Lindquist *et al.*, US Patent Publication No. 20040014662, figures 4 and 9). These findings indicate "modulation of differentiation" in a broad sense, and suggest inhibition of differentiation, as neurospheres are characteristic of undifferentiated neural stem cells and differentiated neurons do not proliferate. The art is silent with regard to enhancement of differentiation of any kind of stem cell by contact with LPL receptor agonists.

The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The specification generally asserts [0038] that effects on differentiation can be studied by analysis of

marker expression. The specification provides examples wherein S1P, alone or in combination with PDGF, inhibits human embryonic stem cell differentiation as indicated by the retention of a stem cell marker in treated cultures. The specification provides no examples wherein these same agents enhance differentiation.

The breadth of the claims and the quantity of experimentation needed: To use the invention as claimed, the skilled artisan would be required to engage in a search for a condition in which a LPL receptor agonist enhances the differentiation of a stem cell. Given that the instant specification and the prior art indicate that the effect of LPL receptor activation is inhibition of differentiation, the skilled artisan must first postulate the existence of a LPL receptor that works in the opposite fashion, demonstrate the expression of this putative receptor on a stem cell, identify the ligand, and characterize the effect of ligand-receptor action. This clearly would require undue experimentation on the part of the person of skill in the art.

14. Claims 1, 3-5, 7-9, 63, 68-70,79, 82, 84-86, 90-93, and 95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

15. Claims 1,3-5,63,79, 82,90-93, and 95 each recite "an agonist of a LPL receptor". According to the specification [0036], "the scope of the present invention includes altered forms of phospholipids and lysopholipids that retain their LPL receptor agonist activity. The scope of

the present invention also includes synthetic peptidic agonists of the LPL receptors." As no categories of chemical structure are excluded from the scope of the term "agonist", dependent claims 7-9, 68-70, and 84-86, by reciting "functional equivalents" of specific phospholipids, expand the genus of agonists to an indeterminate size. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only structural features identified are "altered forms of phospholipids" or "peptidic" and even these general descriptions need not apply to the claimed "functional equivalents". Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

16. In addition, claims 3 and 95 each recite "a ligand of a class III tyrosine kinase receptor". There are no structural limitations on "ligand". The only functional limitation for a ligand is that it binds; it need not activate the receptor. Therefore, the genus of potential ligands extends way beyond the PDGF that was exemplified in the specification, and beyond the known ligands for other class III receptors. Again, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

17. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry,

whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

18. The skilled artisan cannot envision the detailed chemical structure of the encompassed altered forms of phospholipids, peptidic agonists of the LPL receptors, or equivalents thereof. With the exception of PDGF and the class III receptor ligands known in the art (SCF, FLT3L, CSF-1; see Reilly, J. (2003) Blood Reviews 17:2411-248), the skilled artisan cannot envision the detailed chemical structure of the encompassed class III receptor ligands. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

19. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

20. Therefore, only methods comprising S1P, dihydro-S1P, LPA, PAF, SPC, PDGF, SCF, FLT3L, CSF-1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

22. Claims 1,4-9, 13, 14, 41, 63, 66-70, 79, 82-86, 90, and 93 are rejected under 35 U.S.C. 102(e) as being anticipated by Lindquist *et al.*, US Patent Publication No. 20040014662, filed 05/08/2003, with priority to US Provisional Patent application no. 60379114, filed 05/08/2002. The claims are drawn to methods for modulating spontaneous differentiation and producing populations of proliferating undifferentiated stem cells, which method comprises incubating the stem cell in the presence of an agonist of a LPL receptor. Lindquist *et al.* teach (section [0035], for example) a method wherein a cell population comprising mammalian adult neural stem cells is contacted to an agent such as an S1P receptor agonist, LPA receptor agonist, or EDG receptor agonist, (i.e. LPL receptor agonists) for the purpose of stimulating mammalian adult neural stem cell proliferation or neurogenesis, i.e. modulating stem cell differentiation. Lindquist *et al.* specifically teach receptors EDG1, EDG5, and EDG3 (section [0030], which are

synonymous with S1P1, S1P2, and S1P3, respectively, as recited in instant claims 5, 66, and 82. Lindquist *et al.* teach *in vitro* methods for producing populations of proliferating neural stem cells (see claim 34 and figure 4, for examples) in which the LPL receptor agonists are, phospholipids, including S1P (which is a functional equivalent of dihydro S1P). Lindquist *et al.* teach (section [0178] the use of TNF alpha in conjunction with S1P *in vivo*, as recited in instant claim 13. As the modulating agents and target cells are the same, the methods taught by Lindquist *et al.* would inherently result in all of the effects recited in the instant claims, including inhibition of differentiation, as recited in claim 4. Thus the teaching of Lindquist *et al.* fully anticipate claims 1, 4-9, 13, 14, 41, 63, 67-70, 79, 83-86, 90 and 93.

23. Claims 1, 4-9,14, 41, 63, 66-70, 79, 82-86, 90, and 93 are rejected under 35 U.S.C. 102(a) as being anticipated by Harada *et al.*, Society for Neuroscience Abstracts Vol. 27(1), Abstract presented at 31st Annual Meeting of the Society for Neuroscience, November 10-15, 2001. The claims are drawn to methods for modulating spontaneous differentiation and producing populations of proliferating undifferentiated stem cells, which method comprises incubating the stem cell in the presence of an agonist of a LPL receptor. Harada *et al.* teach that undifferentiated embryonic rat neural stem cells express EDG-1, EDG-3, and EDG-5 (S1P1, S1P3, and S1P2, respectively) and that sphingosine-1-phosphate causes these cells to proliferate and display altered morphology. As the modulating agents and target cells are the same, the methods taught by Harada *et al.* would inherently result in all of the effects recited in the instant claims.

Conclusion

24. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C Gamett, Ph.D.,whose telephone number is 571 272 1853. The examiner can normally be reached on M-F, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571 272 0961. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DCG
Art Unit 1647
14 October 2005

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PRIMARY EXAMINER